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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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LEXICON GENETICS INCORPORATED
8800 TECHNOLOGY FOREST PLACE
THE WOODLANDS, TX 77381-1160

EXAMINER	
NICHOLS, CHRISTOPHER J	

ART UNIT	PAPER NUMBER
1647	8

DATE MAILED: 08/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/091,628	WILGANOWSKI ET AL.	
	Examiner	Art Unit	
	Christopher Nichols, Ph.D.	1647	

-- Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 11-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 11-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

1. Applicant's election **without** traverse of Group I (claims 1-3) drawn to an isolated nucleic acid comprising SEQ ID NO: 1 in Paper No. 7 (27 May 2003) is acknowledged.

Status of Application, Amendments, and/or Claims

2. The Preliminary Amendment filed 27 May 2003 (Paper No. 7) has been received and entered in full. Claims 4-10 have been cancelled and claims 11-15 have been added. Claims 1-3 and 11-15 are under examination.

Information Disclosure Statement

3. The information disclosure statement filed 2 July 2002 (Paper No. 5) fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. The information therein has not been considered. No fault is laid on the Applicant. The Examiner invites the Applicant to supply a replacement IDS accompanying the response to this Office Action at no charge.

Oath/Declaration

4. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

Claim Objections

5. Claim **12** is objected to because of the following informalities: claim 12 does not end in a period. Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

6. Claims **1-3** and **11-15** are rejected under 35 U.S.C. 101 because the claimed invention is not supported by a specific, substantial, and credible asserted utility or a well-established utility.

7. The claims are directed to isolated nucleic acid molecule comprising the nucleic acid of SEQ ID NO: 1. The specification discloses nucleic acid molecule SEQ ID NO: 1 which encodes the polypeptide SEQ ID NO: 2. The specification asserts that the polypeptide encoded by SEQ ID NO: 1 is a novel human protein (NHP) that bears structural similarity with mammalian sodium/bile co-transporters (Na^+/bile co-transporters). Hagenbuch and Meier (10 January 2003) "The superfamily of organic anion transporting polypeptides." Biochimica et Biophysica Acta **1609**(1): 1-18 teach that Na^+-bile acid co-transporters belong to a large and structurally diverse superfamily with a broad range of ligand specificity. More specifically, Craddock *et al.* (January 1998) "Expression and transport properties of the human ileal and renal sodium-dependent bile acid transporter." Am J Physiology **274**(1 Pt 1): G157-69 teaches that Na^+/bile co-transporters

are expressed in the ileum, liver, and kidneys of mammals. The liver and ileal Na^+-bile acid co-transporters only share 35% sequence homology while the ileal and renal Na^+-bile acid co-transporters are believed to arise from the same parent gene (pp. G157). Also, the ileal and renal Na^+-bile acid co-transporters differ in their metabolite specificity with the liver Na^+-bile acid co-transporters (G157-G158). The specification does not disclose any data for any activity for the polypeptides encoded by SEQ ID NO: 1. There are no working examples. There are no well-established utilities for newly discovered biological molecules. However, the specification contains several assertions of utilities. Each will be discussed in turn.

a. *The nucleic acid molecule of SEQ ID NO: 1 encodes a novel human protein (NHP):* The Applicant's assertion that SEQ ID NO: 1 encodes a sodium/bile co-transporter is credible because it shares sequence homology with several sodium/bile co-transporters. SEQ ID NO: 1 and the polypeptide SEQ ID NO: 2 share 60.8% and 46.9% homology respectively with known mammalian sodium/bile co-transporters as disclosed by US 5589358 (31 December 1996) Dawson and US 5869265 (9 February 1999) Dawson. It is noted that both US 5589358 and US 5869265 include functional data to validate their claims of the novel gene's identity (Figures 4-6 in both patents). However, this assertion is not specific, as the art recognizes a the family of SLC10 Na^+-bile acid co-transporters as having over 50 members {Hagenbuch and Dawson (8 July 2003) "The sodium bile cotransport family SLC10." European Journal of Physiology (Epub ahead of print) pp. 1-10}. It is not clear from the specification or the claims to which sodium/bile co-transporter is claimed, what tissues are it expressed in, and at what levels. Secondly, the specification's assertion that SEQ ID NO: 1 encodes a novel sodium/bile co-

transporter is not a substantial assertion of utility, since significant further research would be required of the skilled artisan to determine what SEQ ID NO: 1's properties are.

b. *The polypeptide encoded (SEQ ID NO: 2) by SEQ ID NO: 1 have sodium/bile co-transporter biological activity:* The specification asserts that SEQ ID NO: 1 encodes a polypeptide that is a novel sodium/bile co-transporter which based on its structural similarity to prior art of sodium/bile co-transporter that have been characterized. While this assertion is credible it is neither specific nor substantial. It is not specific because this assertion would not have been accepted by one skilled in the art because the art establishes that sodium/bile co-transporter, while structurally similar, are functionally diverse. The art teaches that using known and functionally established clones of a Na^+/bile co-transporter can yield genes of varying sequence homology and different functions. For instance, Lazaridis *et al.* (26 September 2000) "Alternative splicing of the rat sodium/bile acid transporter changes its cellular localization and transport properties." PNAS **97**(20): 11092-11097 teaches that a single gene, the Na^+-dependent bile acid transporter (ASBT), encodes to separate and distinct mature polypeptides, the full-length ASBT is expressed ay the apical plasma membrane of epithelia and imports bile acids while that t-ASBT (a shorter length isoform from the same gene) is expressed on the basolateral member and is responsible for the efflux of bile acids (pp. 11096; Figure 5). Therefore the assertion that SEQ ID NO: 1 encodes a sodium/bile co-transporter is not substantial because the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. The problem of predicting protein structure from sequence data and in turn utilizing predicted structural

determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions [see Wells (18 September 1990) "Additivity of Mutational Effects in Proteins." Biochemistry **29**(37): 8509-8517; Ngo *et al.* (2 March 1995) "The Protein Folding Problem and Tertiary Structure Prediction, Chapter 14: Computational Complexity Protein Structure Prediction, and the Levinthal Paradox" pp. 492-495]. The art clearly shows that structural similarity of different sodium/bile co-transporters is not predictive of expression patterns or functional similarity. Moreover, Oelkers *et al.* (April 1997) "Primary Bile Acid Malabsorption Caused by Mutations in the Ileal Sodium-dependent Bile Acid Transporter Gene (*SLC10A2*)." J. Clin. Invest. **99**(8): 1880-1887 teaches that point mutations L243P and T262M abolished taurocholate and other bile acid transport (Figures 4-6). It is noted that SLC10A2 shares 43.5% sequence homology with SEQ ID NO: 2. Therefore, the specification's assertion that SEQ ID NO: 1 encodes a polypeptide with sodium/bile co-transporter is not a substantial assertion of utility, since significant further research would be required of the skilled artisan to determine what those activities are due the differences in sequence.

c. *The nucleic acid molecule can be expressed in cell lines:* The specification asserts that the nucleic acid molecule is useful for expression in cell lines. This asserted utility is credible, but is neither substantial nor specific. Since there is no substantial utility for the encoded polypeptide, there is also no substantial utility for the transformed cell lines. It would take significant further research to determine if the transformed cells could be used for particular diseases, since no nexus between a disease state and an alteration in SEQ ID NO: 1 expression levels or form (i.e. mutations) has been disclosed in the specification. Further, since all nucleic acids can be used to transform cell lines, this asserted utility is not specific.

d. *The nucleic acid molecule can be used to make chimeric proteins:* Although credible, this asserted utility is not substantial. The instant specification does not disclose any known disease state, toxin, or poison associated with SEQ ID NO: 1 or its activity. Therefore, it is not clear how the skilled artisan would use a chimeric polypeptide for therapeutic, diagnostic, or research uses. Since significant further research would be required to determine how to use the identified chimeric polypeptide, the asserted utility is not substantial. In addition this utility is not specific as any nucleic acid molecule can be used in such a manner {see Sun *et al.* (2 March 2001) "The Rat Liver Na^+/Bile Acid Cotransporter." The Journal of Biological Chemistry **276**(9): 6825-6833}.

e. *The nucleic acid molecule SEQ ID NO: 1 has therapeutic uses:* This is a credible but not substantial asserted utility. The instant specification does not disclose any known disease state, toxin, or poison associated with SEQ ID NO: 1. Therefore, it is not clear how the skilled artisan would use the nucleic acid molecule or oligonucleotides, antisense

polynucleotides, ribozymes, dsRNA, or gene therapy constructs made with SEQ ID NO: 1 for therapeutic uses. Since significant further research would be required to determine how to use the identified polynucleotide, the asserted utility is not substantial. In addition this utility is not specific as any nucleic acid molecule can be used in such a manner.

f. *The nucleic acid molecule is useful as probe or primer:* The specification asserts that the isolated nucleic acid molecule is useful as a probe to detect genes encoding SEQ ID NO: 1 or variants thereof, as primers or hybridization probes in screening libraries, assessing gene expression patterns, use in microarrays, or high-throughput "chip format", solid support matrix/substrate systems, microarray-based analysis, and addressable arrays. This asserted utility is credible, but is neither substantial nor specific. Since there is no substantial utility for the encoded polypeptide, there is also no substantial utility for the nucleic acid probes to identify such. It would take significant further research to determine if the polynucleotide could be used as probes for particular diseases, since no nexus between a disease state and an alteration in SEQ ID NO: 1 expression levels or form (i.e. mutations) has been disclosed in the specification. Further, since all nucleic acids can be used as probes or primers, this asserted utility is not specific.

g. *The nucleic acid molecule can be used in assays for drug screening to identify compounds that modulate nucleic acid expression:* While credible, this asserted utility is not substantial. In such assays, compounds are screened for their ability to up-regulate or down-regulate expression of the nucleic acid molecule. Compounds that have on or the other activity are then labeled as potential drugs. However, the instant specification does not disclose any specific disease state wherein there is a change in SEQ ID NO: 1

expression levels or forms (i.e., mutations). Therefore, it is not clear how the skilled artisan would use a potential drug identified by this method. Since significant further research would be required to determine how to use the identified potential drugs, the asserted utility is not substantial. In addition this utility is not specific as any nucleic acid molecule can be used in such a manner.

h. *The nucleic acid molecule can be used in novel molecular target selection and drug development:* While credible, this asserted utility is not substantial. In such methods, compounds are screened either physically or through computer modeling to determine their ability to bind to the target sequence. Compounds that have on or the other activity are then labeled as potential drugs. However, the instant specification does not disclose any specific disease state wherein there is a change in SEQ ID NO: 1 expression levels or forms (i.e., mutations). Craddock *et al.* (January 1998) "Expression and transport properties of the human ileal and renal sodium-dependent bile acid transporter." Am J Physiology **274**(1 Pt 1): G157-69 teaches that Na^+/bile acid co-transporters vary in their response to metabolites and inhibitors (Tables 1-3; Figures 4-9; pp. G168-G169). Therefore, in light of the absence of a clearly defined isoform and its ligand/metabolite/inhibitor properties, it is not clear how the skilled artisan would use a potential drug identified by this method. Since significant further research would be required to determine how to use the identified potential drugs, the asserted utility is not substantial. In addition this utility is not specific as any nucleic acid molecule can be used in such a manner.

i. *The nucleic acid molecule can be used to make restriction maps and/or to search sequence databases:* While credible, this asserted utility is not substantial or specific. In such methods, the sequence is examined to identify restriction enzyme cleavage sites and then restriction fragments or probes are used to search sequence databases. Sequences that share a certain level of homology thus identified. However, the instant specification does not disclose any specific disease state wherein there is a change in SEQ ID NO: 1 expression levels or forms (i.e., mutations). Therefore, it is not clear how the skilled artisan would use a sequences identified by this method. Also, since SEQ ID NO: 1 has no established biological function, it is not clear to what use the identified sequences could be. Since significant further research would be required to determine how to use the identified sequences, the asserted utility is not substantial. In addition this utility is not specific as any nucleic acid molecule can be used in such a manner.

j. *The nucleic acid molecule is useful to make inhibitory antisense or double stranded oligonucleotides:* Again, although credible, this asserted utility would only be substantial if the encoded polypeptide has a substantial utility. Otherwise, significant further research would be required of the skilled artisan to use the claimed nucleic acid molecules to make inhibitory antisense or double stranded oligonucleotides, since it is unclear when it would be desirable to use the inhibitory antisense or double stranded oligonucleotides. In addition this utility is not specific as any nucleic acid molecule can be used to make inhibitory antisense or double stranded oligonucleotides.

k. *The nucleic acid molecule is useful as probe or primer:* The specification asserts that the isolated nucleic acid molecule is useful as a probe to detect genes encoding SEQ

ID NO: 1 or variants thereof, as primers to amplify corresponding gene fragments, to identify potential genetic disorders, in sequence arrays, to screen collections of genetic material from patients who have a particular medical condition, restriction fragment length polymorphism (RFLP) screens, to screen a human genomic library using PCR and other methods, to search sequence databases, to identify mutations associated with a particular disease, or in anti-sense technology to regulate gene expression of SEQ ID NO: 1. This asserted utility is credible, but is neither substantial nor specific. Since there is no substantial utility for the encoded polypeptide, there is also no substantial utility for the nucleic acid probes to identify such. It would take significant further research to determine if the polynucleotide could be used as probes for particular diseases, since no nexus between a disease state and an alteration in SEQ ID NO: 1 expression levels or form (i.e. mutations) has been disclosed in the specification. Further, since all nucleic acids can be used as probes or primers, this asserted utility is not specific.

l. *The nucleic acid molecule is useful to make a genome library:* Again, although credible, this asserted utility would only be substantial if the encoded polypeptide has a substantial utility. Otherwise, significant further research would be required of the skilled artisan to use the claimed nucleic acid molecules to make a genome library, since it is unclear when it would be desirable to use the genome library. In addition this utility is not specific as any nucleic acid molecule can be used to make genome library.

m. *The nucleic acid molecule (SEQ ID NO: 1) can be used to make polypeptides for analysis, characterization, or therapeutic uses:* This asserted utility is not substantial nor specific. In recombinately expressing a polypeptide, the polynucleotide is transfected

into a host cell and then the protein is recovered. However, the instant specification does not disclose any known function for the claimed polypeptide or any disease state, toxin, or poison associated with SEQ ID NO: 1. In addition, this utility assertion is not specific as it can be applied to any given polynucleotide. Therefore, it is not clear how the skilled artisan would use a polypeptide manufactured by this method, for analysis, characterization, or therapeutic uses. Since significant further research would be required to determine how to use the identified polynucleotide, the asserted utility is not substantial

n. *The nucleic acid molecule can be used in chromosome mapping:* In order to be useful as a chromosomal probe, the precise chromosomal map position must be disclosed. The Specification teaches that SEQ ID NO: 1 is located on chromosome 4. Hagenbuch and Meier (March 1994) "Molecular Cloning, Chromosomal Localization, and Functional Characterization of a Human Liver Na^+/Bile Acid Cotransporter." J. Clin. Invest. **93**(3): 1326-1331 teach the cloning, characterization, and chromosomal location of a rat liver Na^+/taurocholate co-transporting polypeptide (Ntcp) which shares 27.9% homology with SEQ ID NO: 1 (pp. 1331). It is of note that Hagenbuch and Meier performed functional assays to confirm the functional identity of the Ntcp gene thus providing guidance to the skilled artisan to make and use the newly discovered Ntcp (Figures 3 and 4). In the instant application, substantial further research would be required for the skilled artisan to determine where this particular sequence is mapped in order to use the nucleic acid molecule in the asserted utility as a chromosomal map probe.

The asserted utility is also not specific, since the entire class of genes can be asserted to be used in this way.

o. *The nucleic acid molecule is useful for encoding antigenic portions of SEQ ID NO: 2:* This utility is also not substantial, because there is no substantial utility for the full length polypeptide. If substantial further research is required to determine how to use the full-length polypeptide, then substantial further research is also required to determine how to use antibodies generated from antigenic fragments. Also, any nucleic acid molecule can be used in this manner therefore the asserted utility is not specific either.

p. *The nucleic acid molecule (SEQ ID NO: 1) can be recorded on computer readable media:* The instant specification does not disclose any known disease state, toxin, or poison associated with SEQ ID NO: 1 or its activity. Therefore, it is not clear how the skilled artisan would use the computer readable media as identified by this method, for therapeutic or diagnostic uses. Since significant further research would be required to determine how to use the identified nucleic acid or polypeptide, the asserted utility is not substantial. Also, any nucleic acid molecule can be used in this manner therefore the asserted utility is not specific either.

q. *The nucleic acid molecule is useful for making transgenic animals:* No phenotype has been disclosed for such transgenic animals. In the absence of such disclosure, the skilled artisan would have to experiment significantly in order to determine how the transgenic animals could be used. Therefore, the asserted utility is not substantial. Also, any nucleic acid molecule can be used in this manner therefore the asserted utility is not specific either.

8. Therefore, in the absence of a well-established utility, and the absence of a specific, substantial and credible asserted utility, the claimed invention lacks patentable utility under 35 U.S.C. § 101.

9. If Applicant can submit evidence (in the form of a declaration under 37 CFR 1.132 or post-filing date publications) supporting the specification's assertion that SEQ ID NO: 1 has a specific function similar to a known sodium/bile co-transporter, wherein the specific function was predicted by the specification as originally filed, such would be viewed favorably as evidence of patentable utility.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims **1-3** and **11-15** are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

11. Claims **1, 2, 12, 13,** and **15** are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

12. The claims are broadly drawn to include any isolated nucleic acid molecule comprising at least 59 contiguous nucleotides from SEQ ID NO: 1. The language of said claims encompasses all nucleic acids which share at least 100% sequence homology with 59 contiguous nucleotides of SEQ ID NO: 1, with no functional or structural limitations.

13. The specification teaches that SEQ ID NO: 1 encodes SEQ ID NO: 2, a proposed Na^+/bile acid co-transporter. As discussed above, SEQ ID NO: 1 and thus recombinant expression vectors and host cells as well as SEQ ID NO: 2 lack utility.

14. The specification fails to provide any guidance for the successful characterization of SEQ ID NO: 1's encoded polypeptide's function or any fragments thereof and since resolution of the various complications in regards to targeting the role a particular gene in an organism is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the invention using the specification and the state of the art as outlined below, the quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of SEQ ID NO: 1's identity and function. In the absence of any guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

15. Since the specification as filed does not provide any guidance or examples that would enable a skilled artisan to make fragments of SEQ ID NO: 1 with a known utility. Additionally, a person skilled in the art would recognize that predicting the efficacy of using a specific polypeptide function based solely on its sequence homology is highly problematic. Thus, although the specification prophetically considers and discloses identity and function of SEQ ID NO: 1 and its fragments, such a disclosure would not be considered enabling since the state of protein biochemistry is highly unpredictable. The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

16. The following references are cited herein to illustrate the state of the art of protein biochemistry.

17. On the nature of the invention, Wong *et al.* (10 November 1995) "Identification of a Mutation in the Ileal Sodium-dependent Bile Acid Transporter Gene that Abolishes Transport Activity." The Journal of Biological Chemistry **270**(45): 27728-27234 teaches that a single bp change from C to T, resulted in the amino acid change of a serine from proline at position 290 of the ileal Na^+/bile acid co-transporter (Abstract). This single bp change abolished taurocholate transport activity (Figure 4 and 9). Wong *et al.* teach that this single mutation in the ileal

Na^+/bile acid co-transporter could increase susceptibility to some forms of Crohn's disease or worsen symptoms (pp. 27234). Thus the skilled artisan is confronted with a undue burden of experimentation, unpredictability in the results of mutations or sequence changes in Na^+/bile acid co-transporters, and prior art that teaches a single mutation in a ileal Na^+/bile acid co-transporter could be devastating to the bile acid transport activity of the protein.

18. Regarding derivatives and fragments of SEQ ID NO: 1, the problem of predicting protein structure from sequence data for nucleic acids which encode polypeptides and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions [see Wells (18 September 1990) "Additivity of Mutational Effects in Proteins." Biochemistry **29**(37): 8509-8517; Ngo *et al.* (2 March 1995) "The Protein Folding Problem and Tertiary Structure Prediction, Chapter 14: Computational Complexity Protein Structure Prediction, and the Levinthal Paradox" pp. 492-495]. However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of

changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone [Bork (2000) "Powers and Pitfalls in Sequence Analysis: The 70% Hurdle." Genome Research **10**:398-400; Skolnick and Fetrow (2000) "From gene to protein structure and function: novel applications of computational approaches in the genomic era." Trends in Biotech. **18**(1): 34-39, especially p. 36 at Box 2; Doerks *et al.*, (June 1998) "Protein annotation: detective work for function prediction." Trends in Genetics **14**(6): 248-250; Smith and Zhang (November 1997) "The challenges of genome sequence annotation or 'The devil is in the details'." Nature Biotechnology **15**:1222-1223; Brenner (April 1999) "Errors in genome annotation." Trends in Genetics **15**(4): 132-133; Bork and Bairoch (October 1996) "Go hunting in sequence databases but watch out for the traps." Trends in Genetics **12**(10): 425-427]. Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the

unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

19. Thus the specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results sequence homology and prediction to fragments of SEQ ID NO: 1 as exemplified in the references herein.

20. Claims **1, 12,** and **15** are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

21. The claims are drawn to polypeptides having at least 59 contiguous nucleotides with of SEQ ID NO: 1. The claims do not require that the polypeptide possess any particular conserved structure, or other distinguishing feature, such as a specific biological activity. Thus, the claims are drawn to a genus of polypeptides that is defined by sequence identity (such as a stretch of contiguous nucleotides).

22. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making

the claimed product, and any combination thereof. In this case, the only factor present in the claim that is sufficiently disclosed is a partial structure in the form of a recitation of percent identity. The specification does not identify any particular portion of the structure that must be conserved, nor does it provide a disclosure of structure/function correlation. The distinguishing characteristics of the claimed genus are not described. The only adequately described species is a polypeptide comprising SEQ ID NO: 2 and a polynucleotide comprising SEQ ID NO: 1. No active variants are disclosed. Accordingly, the specification does not provide adequate written description of the claimed genus.

23. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

24. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to

lack of written description for that broad class. The specification provided only the bovine sequence.

25. Therefore, only isolated polypeptides comprising the amino acid sequence set forth in SEQ ID NO: 2 and the nucleic acid sequence set forth in SEQ ID NO: 1, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision.

26. Claim **2** is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

27. The term "stringent" in claim 2 is a relative term which renders the claim indefinite. The term "stringent" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Neither the specification nor the art defines the term unambiguously. Thus the metes and bounds of the claims cannot be determined.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

28. Claim **1** is rejected under 35 U.S.C. 102(b) as being anticipated by The Sanger Centre and The Washington University Genome Sequencing Center (1998) "Toward a Complete Human Genome Sequence." Genome Research 8(11): 1097-1108. The Sanger Centre and The Washington University Genome Sequencing Center disclose a nucleic acid sequence which shares 100% sequence homology with bp 1-377 of SEQ ID NO: 1 thus meeting the limitations of claim 1 (see attached sequence search results).

Summary

29. Claims **1-3** and **11-15** are hereby rejected.

GARY KUNZ
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:00AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

CJN
August 6, 2003